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AIDS-Related Cancers in the Era of Highly Active Antiretroviral Therapy

ABSTRACT

Highly active antiretroviral therapy (HAART) has shown great efficacy in reducing human immunodeficiency virus levels, increasing immunity, and prolonging the survival of persons with acquired immunodeficiency syndrome (AIDS). The risk of life-threatening infections has been greatly reduced. However, the impact of HAART on the incidence of malignancy has been less clear. Published studies generally show that the risk of developing Kaposi's sarcoma declined by about two-thirds between 1994 and 1995 and from 1996 onward (considered the HAART era). Even before 1994, the risk for Kaposi's sarcoma in persons with AIDS had declined considerably and this cancer has now become relatively uncommon. The mechanism by which this decline in incidence was achieved appears to involve improved immunity. Data on the reduction in the risk for non-Hodgkin's lymphoma are mixed. Several studies conducted between 1997 and 1999 found no reduction in the risk for non-Hodgkin's lymphoma, although the most recent data (from 1997 to 1999) show a 42% decrease in risk. Even with a one-third reduction, the risk for non-Hodgkin's lymphoma remains considerably elevated. This high risk may be related to the fact that HAART therapy does not restore the immune system to normalcy. The increased lymphocyte turnover, with its accompanying risk of genetic errors, may increase the risk of developing non-Hodgkin's lymphoma. Most reports have insufficient data to analyze the impact of HAART therapy on incidence of central nervous system lymphomas, but recent data (from 1997 to 1999) showed a significant reduction in that risk. The mechanism by which this might occur is unclear because the central nervous system is an immunologic sanctuary. The relatively low incidence of other cancers in persons with AIDS makes it difficult to gauge the effect of HAART on their incidence, but to date, no significant trends have been reported for specific tumor types or for the overall risk of non–AIDS-related cancers.

Kaposi's sarcoma and non-Hodgkin's lymphoma are considered acquired immunodeficiency syndrome (AIDS)-defining illnesses. Although invasive cervical carcinoma is less clearly related to the human immunodeficiency virus (HIV) and/or AIDS, it is also accepted as AIDS-defining.[1] In addition, persons with HIV/AIDS have been found to be at increased risk for several other cancers—most prominently, Hodgkin's disease and anal cancers.[2] Other sites, especially conjunctival tumors and testicular cancer, have also been reported in some registry studies and case reports, although the small increases in the relative risk observed make it difficult to convincingly associate these cancers with AIDS.

The pathogenesis of AIDS-related cancers (ie, Kaposi's sarcoma and non-Hodgkin's lymphoma) is generally considered to be directly related to immunosuppression rather than HIV infection.[3] The logic behind this supposition is compelling. The malignant cells themselves are not infected with HIV. Moreover, persons with HIV are not at exceptional risk for these cancers (at least at a detectable level) unless they are also immunosuppressed. In addition, persons who are immunosuppressed for reasons other than HIV infection (eg, iatrogenic or genetic causes) are at risk for these same types of cancer. Some investigators suggest that Tat, a protein expressed by HIV, may be linked to the increased incidence of Kaposi's sarcoma,[4] but even if this proves correct, this incidence is greatly increased only among those in whom there is concomitant immunosuppression.

If immunosuppression underlies the occurrence of these malignancies, then ameliorating the immunodeficiency should markedly reduce the risk of developing cancer. The advent of highly

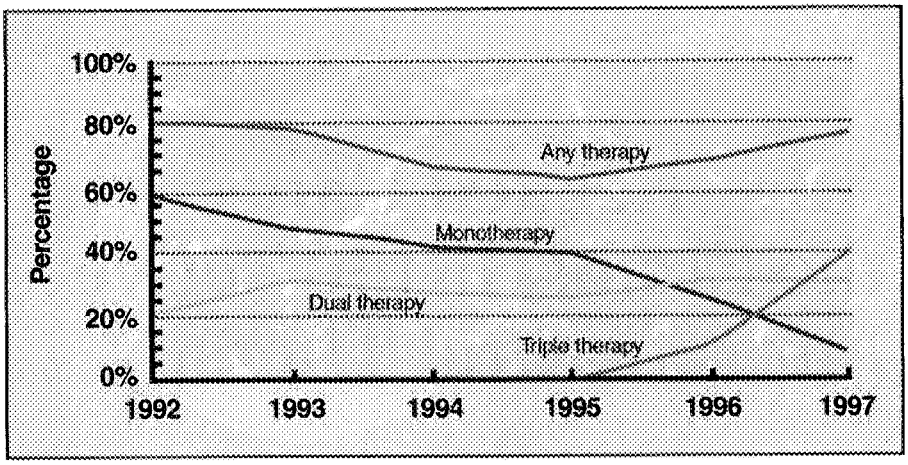

Figure 1: Adult/Adolescent Spectrum of HIV Diseases—The proportion of human immunodeficiency virus (HIV)-infected adults and adolescents with CD4 counts < 500 cells/μL who had antiretroviral therapies prescribed from 1992 to 1997. Zidovudine was introduced as monotherapy beginning in 1987, and dual therapies were introduced in 1990. There are no consistent data about the use of antiretroviral therapy in the general population of persons with acquired immunodeficiency syndrome between 1987 and 1991. Data from the Centers for Disease Control and Prevention.[11]

active antiretroviral therapy (HAART) for persons with AIDS presents the opportunity for examining this hypothesis. Strong evidence exists that HAART results in impressive reductions in HIV replication and is usually associated with improvements in the CD4 lymphocyte counts of persons with immunosuppression.[5] As expected, these improvements in immunity have greatly reduced the incidence of AIDS-associated opportunistic infectious diseases.[6] In this review, we will examine the evidence that they have also decreased the incidence of cancer in persons with AIDS.

Antiretroviral Therapies

The extent to which antiretroviral therapies might influence HIV-related immunosuppression depends on their efficacy in improving immunity and how widely such therapies are used in persons with HIV/AIDS. In 1987, monotherapy with zidovudine (azidothymidine or AZT [Retrovir]) was shown to be effective in improving prognosis.[7] The clinical response was justifiably attributed to improvements in immunity as measured by increasing CD4 cell counts, although it is also possible that lowering HIV levels further improved immunity by affecting functional immunity in still-viable lymphocytes.[8]

In practice, clinicians soon observed that the improvement in immunity following zidovudine therapy was transitory. Within 6 to 12 months, therapy-resistant HIV variants emerged, high viral levels returned, and the deterioration of immunity resumed. Later studies confirmed that the long-term benefit was minimal,[9] and the need for combination antiretroviral regimens became obvious.

During the 1990s, many new antiretroviral agents were licensed, and others continue to be developed. The introduction of effective protease inhibitors in the mid-1990s has been especially important. Clinical trials have demonstrated that these drugs, used in combination, are highly effective in blocking HIV replication for prolonged periods.[10] In many persons, viral levels fall below the level at which they can be detected even with sensitive tests.

Highly Active Antiretroviral Therapy

Dual drug therapies also came into wide use in the early 1990s, and since 1996, triple-drug regimens that include protease inhibitors have been recommended for persons with clinically significant HIV-related immunosuppression. Figure 1, based on data reported by the Centers for Disease Control and Prevention (CDC),[11] illustrates the proportion of persons with HIV/AIDS who were taking these drugs in the United States between 1992 and 1997.

Highly active antiretroviral therapy with protease inhibitor drugs blocks HIV replication, resulting in meaningful improvements in the clinical status and prognosis of many persons infected with HIV. This strategy demonstrates that good HIV control and an increase in the CD4 count are associated with enhanced improvement in defending the host against environmental pathogens. Moreover, these results have revolutionized the care and prognosis of HIV patients, leading to the reasonable expectation that persons with HIV infection can survive for many years, even after an AIDS diagnosis.

Despite these encouraging developments, there are several serious caveats concerning the impact of HAART therapy on cancer risk trends. Foremost is the fact that many HIV-infected persons are not receiving HAART.[11] Some people are not aware that they are HIV-infected until they develop an AIDS-defining illness (which may be cancer). For others, such as those with dementia or drug addiction problems, the complex regimens are beyond their ability to support or maintain. Still others cannot tolerate the side effects of the drug combinations. Finally, even among those who take full HAART regimens, breakthrough HIV infections from resistant strains can occur.

It is reasonable to hope that newly developed antiretroviral drugs will lead to easier administration, lower toxicities, and control of HIV viremia. In the interim, however, there continues to be a population of HIV-infected, immunosuppressed persons who are not receiving effective anti-HIV therapy.

Immune Response Does Not Normalize

Even among those who respond well to HAART, the immune responses of severely immunocompromised subjects typically do not return to normal. Rather, in seriously immunocompromised subjects, CD4 counts increase from dangerously low levels of less than 50 cells/μL to perhaps 200 to 300 cells/μL.[12] At this level, immunity is not normal (normal CD4 levels are above 500 cells/μL), but the risk of develop-

ing a major life-threatening disease is much less.

One unexpected consequence of HAART's success is the increasingly recognized phenomenon of immune reconstitution disease, in which symptoms appear in direct relation to the improvement in immunity.[13,14] In these syndromes, the host recognizes and reacts to low-grade infections that were not apparent earlier, such as may occur with *Mycobacterium avium-intracellulare* and hepatitis C virus. This reaction can be so severe as to be fatal. Thus, the immunity that is measured as marginally deficient by conventional CD4 counts can have highly reactive clones that are proliferating robustly because of stimulation from smoldering infections. These activated clones may affect the risk of developing cancer, especially the lymphomas, in ways that obscure a relationship to HAART.

Kaposi's Sarcoma

The proportion of AIDS patients presenting with Kaposi's sarcoma has declined over time. There are several explanations for this change. Public health data often record only the first AIDS-defining illness. Early in the AIDS epidemic, most AIDS cases were identified on the basis of a diagnosis of Kaposi's sarcoma or *Pneumocystis carinii* pneumonia. However, as the understanding of the range of AIDS-associated diseases increased, the definition of AIDS expanded to include other conditions.

In the most recent definition of an AIDS case, formulated in 1993, the CDC changed the definition to include HIV-infected persons who have no overt illness but are immunosuppressed (CD4 < 200 cells/μL or < 14%) to the point of being at risk for an AIDS-defining illnesses.[1] This expansion of the diagnosis has allowed recognition of other conditions as being AIDS-related before the appearance of Kaposi's sarcoma.

Even in data sets that include both onset and a later diagnosis of Kaposi's sarcoma, however, the incidence of the disease has declined. Some of this decline can be attributed to changes in the population of HIV-infected persons in the United States. Among persons with AIDS, the incidence of Kaposi's sarcoma varies considerably by group. Initially, the majority of AIDS cases occurred in homosexual men, a group with an 8- to 10-fold higher risk for Kaposi's sarcoma than other groups.[3] Moreover, most cases were in white men, a group that has at least twice the risk for Kaposi's sarcoma compared to black men, even after controlling for HIV-exposure groups. However, the population of AIDS patients who are white homosexual men has declined as a proportion of all AIDS cases, whereas the percentage who are black men, both homosexual and otherwise, has increased, thus progressively enriching the mix of newly diagnosed AIDS cases with persons at lower risk for Kaposi's sarcoma. The impact of HAART on risk for Kaposi's sarcoma needs to be assessed carefully against this backdrop.

Kaposi's Sarcoma and HAART

Almost all reports have noted declines in the incidence of Kaposi's sarcoma between the early 1990s and the post-1996 era (Table 1).[15-21] In summary, between 1994 and 1995 and from 1996 onward (the HAART era), the incidence of Kaposi's sarcoma declined by about two-thirds, to the point that it is now an uncommon diagnosis in people with AIDS.

However, a temporal approach does not prove a relationship to HAART because the decline in Kaposi's sarcoma incidence long preceded the introduction of this therapy. In part, the change in the definition of AIDS and shifts in the population that became infected with HIV contributed to that decline, as discussed above. Additionally, the early, less effective, antiretroviral regimens may have reduced the incidence of Kaposi's sarcoma, although statistical evidence supporting this association is inconclusive.[15]

More speculatively, we now understand that Kaposi's sarcoma requires infection with a newly described herpesvirus, HHV-8,[22] which is common among homosexual men.[23] This virus appears to have been co-epidemic with sexually transmitted HIV.[24,25] Possibly, burnout of the HHV-8 epidemic, along with exhaustion of the population susceptible to Kaposi's sarcoma, could have contributed. Persons who acquire HHV-8 while HIV-infected (and presumably immunosuppressed) have a 2.5-fold increased risk of developing Kaposi's sarcoma over that of persons who were already infected with HHV-8 when they became infected with HIV.[26]

Impact on Immunity

Nevertheless, there is compelling extrinsic and intrinsic evidence that improved immunity is probably the major factor influencing the reduction in the incidence of Kaposi's sarcoma. Extrinsically, case reports describe improvement or even resolution of preexisting Kaposi's sarcoma in persons who began receiving HAART.[27-31] Some reports suggest that this clinical effect is particularly potent in combination antiretroviral drug regimens containing protease inhibitors.[30,31]

Given its impact on existing Kaposi's sarcoma tumors, treatment with HAART would be expected to prevent incipient tumors. Intrinsically, in several published reports, the "breakthrough" cases of Kaposi's sarcoma that occurred in the HAART era were observed only among men who did not receive potent antiretroviral therapy.[15,20]

Also supporting a direct role for HAART (through its impact on immunity) is a report that examined the risk of illnesses in HIV-infected persons started on HAART. Investigators from the Swiss HIV Cohort Study examined the risk for Kaposi's sarcoma and other diseases.[32] Case numbers are somewhat marginal for strong conclusions, but their results showed a significant difference in the incidence of Kaposi's sarcoma between the 6 months just before HAART and the 6 months immediately after HAART.

This decline in incidence implied that HAART had an almost immediate impact. Overall, the risk declined by 66% during the 15 months after HAART was initiated ($P = .001$, compared to the pre-HAART period). While such data are subject to analysis

Table 1

Summary of Data on the Changes in the Incidence of Kaposi's Sarcoma and Non-Hodgkin's Lymphoma in the HAART Era[a]

Investigators	Study Group	Patient Population	Dates	Kaposi's Sarcoma Incidence[b]	Kaposi's Sarcoma Change	Non-Hodgkin's Lymphoma Incidence	Non-Hodgkin's Lymphoma Change
Jones et al[15][c]	Adult/Adolescent Spectrum of HIV Diseases	On therapy	1994–1995	45		15	
			1996–6/97	18	–60%	11	–27%
		Not on therapy	1994–1995	55		16	
			1996–6/97	52	–6%	12	–23%
Jacobsen et al[20][d]	Multicenter AIDS Cohort	Presenting with illness	1994–1995	16		7.9	
			1996–1997	7.5	–47%	7.5	–5%
Buchbinder et al[17][e]	San Francisco City Clinic Cohort	Seroconverters	1993–1995	35		15	
			1996	0	—	19	+27%
Rabkin et al[19][f]	AIDS Clinical Trial Group Studies	Protocol patients	1992–1995	27		6	
			1996–2/97	0.3	–99%	4	–33%
Imperial Cancer Research Fund[21][g]	International Collaboration on HIV and Cancer	Meta-analysis of multiple cohorts	1992–1996	15		6.2	
			1997–1999	5	–67%	3.6	–42%
Grulich[18][h]	Australian National Data	Population data	1993–1997		–55%		–37%
Sparano et al[16][i]	Montefiore Medical Center	Clinic patients	1995–1997		–36%		–67%

[a]The HAART era was considered as starting in 1996. Although HAART therapy was potentially available in 1996, the proportion of subjects who received effective therapy was unclear in most studies.

[b]Incidence rates per 1,000 person-years of follow-up.

[c]Data recorded as Kaposi's sarcoma and individual non-Hodgkin's lymphoma types. Data sum all non-Hodgkin's lymphoma types and average the incidence over the period. In 1994, 16% were on combination antiretroviral therapy (two or more drugs); in 1997, 57% were on combination therapy with 24% being on triple therapy.

[d]Data for 1994–1995 estimated from investigators' Figure 1. For 1989–1995, authors estimate a 71% reduction in the incidence of Kaposi's sarcoma and a 36% increase in the incidence of non-Hodgkin's lymphoma. Among subjects in this study, in 1996 and 1997, respectively, approximately 38% and 48% received combination therapy that included a protease inhibitor.

[e]Relatively small observation time in HAART era. In 1996, 49% were on combination therapy; 30% of subjects had received protease inhibitors.

[f]Only one trial (trial #320 with 915 person-years of follow-up) occurred in the HAART era. In this trial, 50% received a protease inhibitor containing combination therapy.

[g]This re-analysis includes data given in some cohorts described below. HAART was "widely used by 1997."

[h]In specific Australian cohorts, between 25% and 90% of persons with HIV were taking combination therapies in 1997.

[i]Data were not population based. During the same period, outpatient visits declined by 38%. In a small survey of outpatients conducted in 1997, 80% were receiving combination therapies, and 55%, triple therapy.

AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus.

problems that complicate their interpretation,[33] they nevertheless demonstrate a decreased risk for Kaposi's sarcoma specifically related to HAART in a study in which each subject served as his or her own control.

Supplemental Study

As a supplemental study for this report, I examined cancer risk in 309,365 persons with AIDS in the AIDS-Cancer Match Registry Study.[34] More than 21,000 cases of Kaposi's sarcoma were reported in AIDS patients, the majority of which were AIDS-defining illnesses. Cancer incidence in persons with AIDS cannot be easily quantified when the cancer defines AIDS onset, because the number of subjects at risk is unknown. However, persons with AIDS-defining conditions other than Kaposi's sarcoma can be used to define a true cohort, in which incidence can be determined. To limit loss to follow-up bias, the analysis was confined to the 2-year period (4 to 27 months) after the onset of AIDS.

In data presented in Figure 2, the analysis was further restricted to white men so as to minimize the impact of race and sex, and age was adjusted to accommodate temporal changes in the age distribution of the men developing AIDS. The time span permitted a comparison of incidence determinations for the pretherapy periods (1980–1983 and 1983–1986), the era of monotherapies (1987–1989), and the time when dual therapies were available (1990–1993 and 1994–1996). Cancer data were available for only a few of the registries through 1996, and cancer risk in the true triple-therapy HAART era is therefore incomplete. Except for the earliest period, the number of Kaposi's sarcoma cases in each period was impressive (total: 5,312 in homosexual men and 563 in heterosexual men).

After the introduction of zidovudine in 1987, the incidence of Kaposi's sarcoma declined steadily until the last data group in 1994–1996 (Figure 2). This decline might have been affected by changes in therapy, because antiretroviral strategies continued to improve in each period after 1986 and also became more widely distributed.

It should be noted that when the last available data for this analysis were

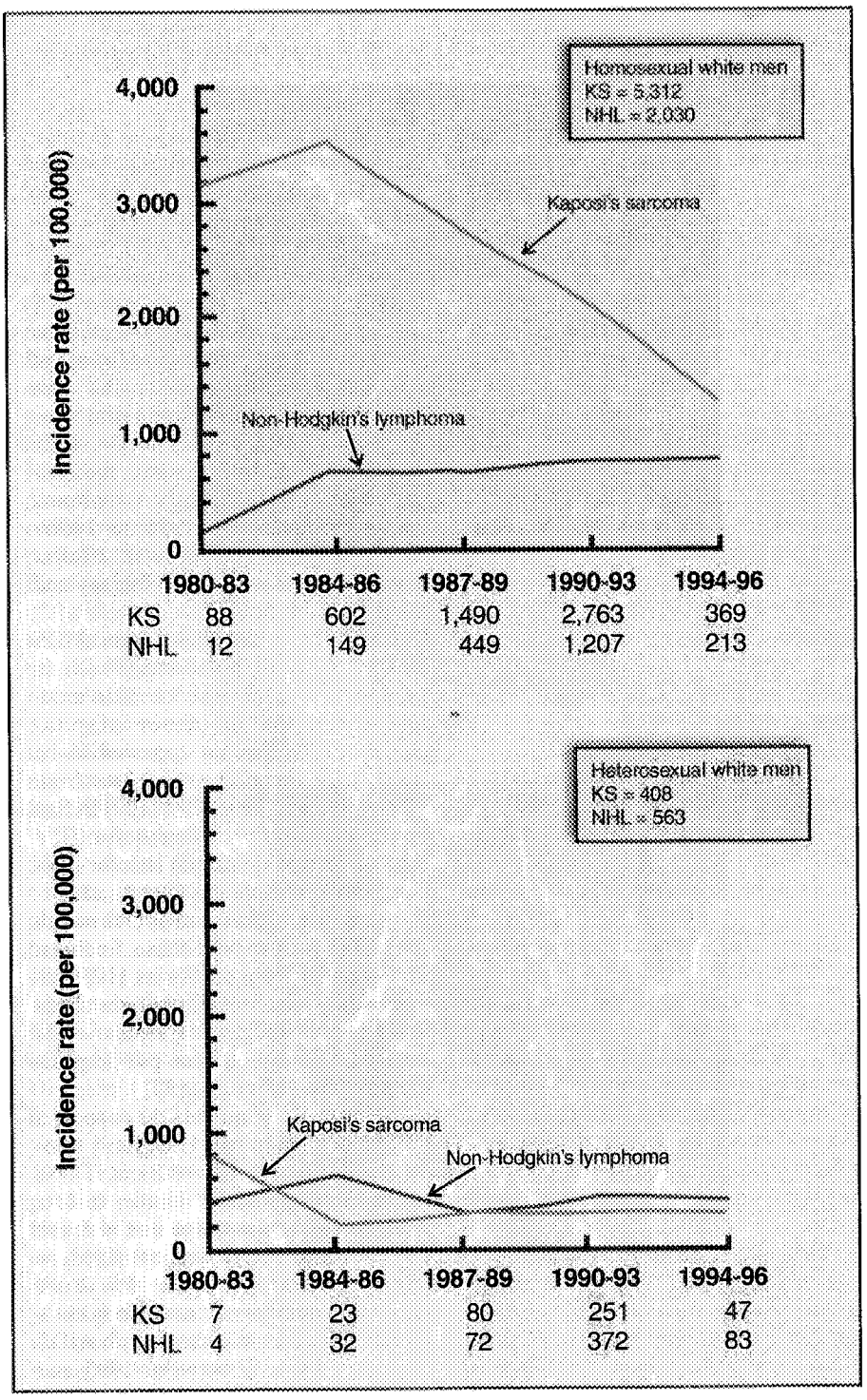

Figure 2: Incidence of Kaposi's Sarcoma and Non-Hodgkin's Lymphoma—Changes in the incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) among white men 4 to 27 months after the onset of acquired immunodeficiency syndrome (AIDS), by homosexual vs heterosexual status. Subjects were excluded if they had previously had a cancer of this type. The number of persons with Kaposi's sarcoma and non-Hodgkin's lymphoma are listed beneath each range of years. To accommodate temporal changes in the age distribution of men developing AIDS, data have been age-adjusted to the world standard population. Data from Frisch et al.[34]

generated (1994–1996), relatively few men would have received protease-containing antiretroviral therapy. However, the proportion of men who received optimal HIV-suppressive therapies would likely have been higher among white homosexuals (the group at highest risk for Kaposi's sarcoma) than in the general population of white heterosexuals.

Thus, the evidence strongly suggests that HAART has further reduced the incidence of Kaposi's sarcoma. That incidence declined by about two-thirds from 1994–1995 to 1996 and later, when HAART became widely available. This decline occurred when the incidence of Kaposi's sarcoma in persons with AIDS had already decreased from earlier years. Kaposi's sarcoma is now uncommon among persons with AIDS who are receiving effective antiretroviral therapy.

Non-Hodgkin's Lymphoma and HAART

The etiology of non-Hodgkin's lymphoma is poorly defined. However, there is no doubt that non-Hodgkin's lymphomas occur at high rates (200- to 300-fold excess) among persons with AIDS.[3] Several observations illustrate that this high incidence is related to dysregulation of the immune system: First, since they are B cells, the lymphoma cells are not infected with HIV. Second, increases in incidence are only measurable in persons with immunosuppression. Third, as with Kaposi's sarcoma, non-Hodgkin's lymphomas are associated with immune disorders in persons not infected with HIV.

However, the critical component may not be immunosuppression. I have argued that the high incidence of AIDS (and other immunosuppressive conditions) could be related to nonlethal genetic errors accumulating in proliferating lymphoid cells, as components respond to the many challenges generated by HIV-related damage,[3] a point also made elsewhere.[18] Over time, a particular cell will acquire a sufficient constellation of errors to escape normal regulation—either partially or irreversibly. Thus, persons with HIV who have lymphoid cells actively replicating in response to antigens will continue to be at higher risk for lymphoma, even if they are receiving HAART, unless their immunity is fully restored.

Impact on Incidence

The impact of HAART on the incidence of non-Hodgkin's lymphoma has varied in different studies (Table 1). In most studies, data on the specific subjects who received HAART therapy are lacking, but it is assumed that subjects in need had access to HAART from 1996 onward. In CDC data from the Adult/Adolescent Spectrum of AIDS Diseases, participants who were taking combination antiretroviral therapies during each semester of the study were identified. In that study, the incidence of non-Hodgkin's lymphoma declined from 1994–1995 to 1996–1997, but the decline was similar among those who received therapy and those who did not.[15]

Similarly, in the Multicenter AIDS Cohort Study of homosexual men (a group with exceptional access to medical care), the incidence of non-Hodgkin's lymphoma appeared to be stable in a comparison of data from 1994–1995 and 1996–1997.[20] In San Francisco, after adjustment for HIV seroconversion dates, the risk for non-Hodgkin's lymphoma increased, although not significantly, through 1996.[17] In line with these findings, investigators from the Swiss HIV Cohort Study also found that the incidence of non-Hodgkin's lymphoma was reduced by only 5% from pre- to post-therapy onset ($P = .31$).[32]

In contrast, some data do support a modest decline in non-Hodgkin's lymphoma during the HAART era. These studies were generally smaller or less well defined than those that did not observe a significant decline. At Montefiore Medical Center in New York City, the number of non-Hodgkin's lymphoma cases in persons with AIDS decreased by 63% between 1995 and 1997, when HAART became available. This decrease was greater than that seen for Kaposi's sarcoma (36%) during the same period and occurred at a time when outpatient HIV/AIDS visits to this hospital increased.[16]

Among participants in amalgamated AIDS clinical trials, the incidence of non-Hodgkin's lymphoma declined by 33%.[19] In Australia, where access to AIDS medications is government supported, national AIDS data show a significant decline (36%) in the number of non-Hodgkin's lymphoma cases reported between 1994 and 1997, but the decline was less than that seen in other AIDS-related diseases.[18]

Meta-analysis of Numerous Prospective Cohorts

To obtain a more powerful analysis, investigators from Oxford University recently undertook a meta-analysis of data from 23 large prospective cohorts in North America, Europe, and Australia.[21] This large database, with 136,000 person-years of observation time, included several of the studies described above. They reported a significant decline (42%) in the incidence of non-Hodgkin's lymphoma, which might be related to HAART. In support of this possibility, there were consistent declines in different areas of the world and in different exposure groups. Importantly, compared with earlier reports, their updated database included incidence results from 1997 to 1999, which is later in the HAART era than data from other studies.

The 42% decline in non-Hodgkin's lymphoma that these investigators observed in the period from 1992 to 1996 was highly significant. Specifically by histology, a decline in incidence was observed for immunoblastic lymphomas but not Burkitt's lymphoma, although the investigators acknowledged that their cohorts had relatively few cases of Burkitt's lymphoma. Thus, the declining risk for non-Hodgkin's lymphoma may represent a finding that is emerging in recent data.

The AIDS-Cancer Match Registry Study

We also examined the incidence trends for non-Hodgkin's lymphoma in the AIDS-Cancer Match Registry Study.[34] The study principles and limitations were similar to those outlined above for Kaposi's sarcoma, focusing on cohorts followed in the 2-year period after the onset of AIDS.

Unlike Kaposi's sarcoma, which has declined steadily since the early years of the AIDS epidemic, the incidence of non-Hodgkin's lymphoma remained fairly stable in both homosexual (2,030 cases) and heterosexual (563 cases) white men throughout every period through 1994–1996 (Figure 2). Rates were about twofold higher in homo-

sexual than in heterosexual white men, possibly reflecting the poorly understood socioeconomic differences that affect risk for non-Hodgkin's lymphoma outside the AIDS setting.[3] However, the incidence of non-Hodgkin's lymphoma did not decline in either group through 1994–1996 (Figure 2).

Unlike the clinical experience with Kaposi's sarcoma, HAART does not appear to have had a consistent impact on existing non-Hodgkin's lymphoma in persons with AIDS. In meeting abstracts, there are a few case reports suggesting that there may be a regression of existing non-Hodgkin's lymphoma,[35,36] but this effect has not been generally observed. Therefore, there is no extrinsic reason to suppose it would have an impact on an incipient lymphoma.

However, improvements in immunity might still affect precancerous clonal expansions that are being driven either by HIV or by antigens from the secondary infections enabled by a weakened immune system. Hence, a reduction in the rate of lymphocyte replication could indirectly reduce the likelihood of developing the genetic errors that lead to cancer. This, in turn, would result in a lower risk of cancer. That said, once non-Hodgkin's lymphoma has manifested, HAART appears to have little impact.

The fact that the immune system is not fully reconstituted in the majority of HAART-treated persons with HIV/AIDS may modify the impact of HAART on the incidence of non-Hodgkin's lymphoma. The partially compensated immune system can become highly activated by new or residual infections, as happens overtly in the immune reconstitution syndromes mentioned above.[13,14] How commonly activation occurs in a more covert manner, with a smoldering lymphocyte proliferation of stimulated clones, is unknown. To the extent that this occurs, the impetus for the development of lymphoma will continue, thereby maintaining the increased incidence of non-Hodgkin's lymphoma.

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Even with a one-third reduction in the risk of non-Hodgkin's lymphoma, the incidence remains considerably elevated.

Central Nervous System Lymphomas

Lymphomas of the central nervous system (CNS) comprise a special subset of malignancies that may be affected by HAART therapy. The relative risk for this disorder is exceptionally high in both children[37] and adults[2] with AIDS. One abstract report suggests that existing CNS lymphoma might respond to treatment with HAART,[38] although given the supposed immunologic sanctuary of the central nervous system, it is difficult to postulate how this effect might occur. Because of the relatively low incidence of the disease, most studies do not have a sufficient number of cases to analyze trends. Nevertheless, it is the general impression that the incidence is declining, as in case data from New York in which biopsy-proven CNS lymphoma decreased by 67% between 1995 and 1997.[16]

This impression is strongly supported by recent findings in international cohorts, in which primary brain lymphoma declined significantly (by 58%) between 1992–1996 and 1997–1999.[21] In addition, the CDC study, with more than 26,000 person-years of follow-up, found that among treated subjects, the incidence of CNS non-Hodgkin's lymphoma declined from 6.22 to 1.8 (71%) per 1,000 person-years between 1994–1995 and 1996–1997.[15] However, among untreated persons with HIV infection, CNS non-Hodgkin's lymphoma started at a lower incidence but also declined, from 4.6 to 3.6 (22%) per 1,000 person-years in the same periods, which complicates interpretation of the favorable result among treated persons.

Assuming the declining incidence of CNS non-Hodgkin's lymphoma is confirmed, it is unclear how this effect is mediated. Over time, reporting practices may have affected data on CNS lymphomas. These lymphomas are difficult to diagnose and require histopathology to distinguish them from other CNS infections that can mimic their symptoms in persons with AIDS. Central nervous system lymphomas are also rapidly fatal, and as with other end-stage AIDS conditions, biopsies may not provide a full evaluation of patients with symptoms. Finally, when the histology is recorded, the information available in the cancer registry data may not include the site of the lymphoma. Given the uncertainty of these data, interpreting trends in the risk for CNS lymphoma is difficult.

Inconsistent Evidence

In summary, evidence supporting a decline in non-Hodgkin's lymphoma risk is inconsistent. In studies that report a declining incidence, the decrease is usually more modest than the declines seen for Kaposi's sarcoma. In the most recent data from the meta-analysis, a 42% reduction in risk was observed,[21] but even with this decline in risk, the incidence still remains much higher than that in the general population not infected with HIV. Reports of declining rates of CNS lymphoma in recently collected data need to be evaluated further.

As the survival of persons with AIDS is prolonged by treatment with HAART, the contribution of non-Hodgkin's lymphoma from AIDS to the overall burden of the disease will be maintained or even increased. Certainly, as the risk for Kaposi's sarcoma declines, non-Hodgkin's lymphoma will increasingly dominate the cancer profile in persons with AIDS.

Other Cancers

The incidence of other cancers in persons with AIDS is too low to demonstrate that changes might be related to HAART. Even without HAART, it has been difficult to ascertain that these cancers occur significantly more often in persons with AIDS. To be considered AIDS-related, the incidence of cancer must be significantly increased in persons with HIV/AIDS, and the increasing incidence must align with a significant trend of rising relative risks as AIDS approaches and passes.[34] The latter criterion is necessary to ensure that the increase is not simply due to a lifestyle that is associated with greater exposure to other known carcinogens.

Persons in several major HIV-exposure groups, such as homosexual men and intravenous drug users, are likely to be risk-takers who smoke more

heavily, have more sex partners (and, therefore, have more exposure to human papillomavirus [HPV]), or use shared needles (and, therefore, have a higher incidence of hepatitis B or C). To the extent that these factors occur excessively in the same populations that become infected with HIV, they would also have excessive smoking- and virus-related cancer risks that are not related to HIV or immunosuppression.

Hodgkin's Disease and the Anogenital Cancers

Of these other cancers, Hodgkin's disease and the anogenital cancers would be the most likely to occur more often in persons with HIV/AIDS. The etiology of Hodgkin's disease is poorly understood, and it is therefore difficult to predict how the partial improvements in immunity achieved with HAART might affect its incidence. Because of the low incidence, large studies will be required.

In the meta-analysis of large HIV cohorts, the risk for Hodgkin's disease was 23% lower in the HAART era, but this decline was not statistically significant.[21] If the incidence of Hodgkin's disease were indeed lower with HAART, this finding would be consistent with a role for some unknown infectious causality that is affected by immunity. However, Hodgkin's disease may share the same unknown causality profile of other non-Hodgkin's lymphomas.

Human papillomavirus infection is recognized as being etiologically important in causing squamous cell anogenital cancers.[22,39,40] In persons with AIDS, increases in dysplasia result from poorly controlled HPV infections,[22,40] and improvements in immunity will likely result in better control of this virus and presumably a lower incidence of anogenital cancers. In the meta-analysis of multiple cohorts, the incidence of cervical cancer increased ($P = .07$) between the 1992–1996 and 1997–1999 periods,[21] but this increase was based on small numbers and occurred at a time when invasive cervical cancer had just been accepted as being AIDS-defining.

As the survival of persons with AIDS who have dysplasias related to HPV is prolonged, the number of anogenital cancers in persons with AIDS may also rise.[40] AIDS-related immunosuppression could lead to loss of control of hepatitis B and C viruses, both of which are linked to the etiology of liver cancer.[41] However, it has not been established that the risk of liver cancer increases as a result of HIV infection or immunosuppression.

Conclusions

The limited number of cancer types—Kaposi's sarcoma and non-Hodgkin's lymphoma, predominantly—found to occur excessively in persons with AIDS argues that immunity, at least the type dysregulated by HIV infection, plays no major role in controlling the occurrence of most common cancers.[3] In the Oxford meta-analysis, the rate of all non–AIDS-related cancers was essentially unchanged (rate ratio = 0.96) despite the improved therapy available to AIDS patients by 1997–1999.[21] However, the decreases in cancer incidence (even in Kaposi's sarcoma and non-Hodgkin's lymphoma) seen with improved immunity might not be related to an immunologically mediated effect on cancer cells.

In Kaposi's sarcoma, immunologic control of HHV-8 could reduce virus-associated proliferation of spindle cells. In non-Hodgkin's lymphoma, HAART-controlled HIV replication prevents further deterioration of the immune system and, with that, the stimulus for lymphoid cell replication declines. Thus, these changes could occur because there is less stimulation of cell replication mechanisms rather than because of any direct effect on cancer itself.

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The Biggar Article Reviewed

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The National Cancer Institute's Dr. Robert Biggar has probably studied the impact of the acquired immunodeficiency syndrome (AIDS) epidemic on cancer trends at least as thoroughly as anyone in the field. His long-term experience is reflected in this comprehensive and well-written overview, which summarizes the evidence concerning highly active antiretroviral therapy (HAART). Indeed, patients are developing fewer opportunistic infections and living significantly longer than they did before the advent of these potent anti–human immunodeficiency virus (HIV) drugs. However, the question remains as to what extent this treatment might also change the incidence of cancers?

Loss of Immunologic Control

In light of the connection between HIV infection and loss of immunologic control, many researchers expected the incidence of more cancers to be increased in HIV-positive individuals than 20 years' experience with HIV and AIDS has actually shown. Greatly increased relative risk estimates have been documented only for Kaposi's sarcoma and non-Hodgkin's lymphoma, whereas other cancers with a potential infectious etiology, such as Hodgkin's disease, anogenital cancers, hepatomas, gastric cancer, and testicular cancer have shown much more moderate risk associations.

Some of these surprising findings are likely explained by the influence of other factors present in groups at high risk for HIV infection. Nevertheless, a long-held argument for the lack of more cancers being convincingly increased by the advent of HIV-induced immunodeficiency is that infected persons do not live long enough for some of the more solid cancers to manifest and become clinically apparent.

HAART Therapy

With the introduction of HAART and related therapies, this condition for a longer life expectancy has been met. However, as Dr. Biggar points out, cancer trends in recent years (ie, the HAART era) are essentially unchanged, and, if anything, show a slight decrease primarily as a result of a decrease in the incidence of Kaposi's sarcoma and perhaps also non-Hodgkin's lymphoma. There is no indication that new cancers are becoming more frequent. We are, however, still in the early phase of a new era, and it is too early to draw any conclusions about what cancers might be part of the